

Paper 8

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WASHINGTON HARBOUR  
3000 K STREET, N.W., SUITE 500  
WASHINGTON, D.C. 20007-5109  
TELEPHONE: (202) 672-5300  
FACSIMILE: (202) 672-5399

SACRAMENTO  
SAN DIEGO  
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TAMPA  
WASHINGTON, D.C.  
WEST PALM BEACH

WRITER'S DIRECT LINE  
(202) 945-6006

EMAIL ADDRESS  
RLTaylor@foleylaw.com

CLIENT/MATTER NUMBER  
029623/0109

April 26, 1999

VIA HAND DELIVERY

Examiner David Saunders  
Crystal Mall One - 7th Floor  
1911 South Clark Street

Re: MICROFABRICATED, FLOWTHROUGH POROUS APPARATUS FOR  
DISCRETE DETECTION OF BINDING REACTIONS

Dear Examiner Saunders:

This is to follow up on our conversation of last week regarding Serial No. 09/063,356. You will find enclosed copies of all Office Actions and Responses from the parent case, Serial No. 08/631,751.

Also enclosed are many of the references cited on the Information Disclosure Statement dated July 8, 1996. As the parent case has been patented, we have removed many such documents from our file. I have sent copies, however, of everything that is available to us at this time.

If you require any further assistance in this matter, please do not hesitate to contact me at (202) 945-6006.

Very truly yours,



Rebecca L. Taylor  
Paraprofessional

Enclosure(s)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kenneth L. Beattie

Appl. No. 08/631,751

Filing Date: April 10, 1997

For: **Microfabricated, Flowthrough  
Porous Apparatus for Discrete  
Detection of Binding Reactions**

Art Unit: 1818

Examiner: Bakalyar, H.

Atty. Docket: HARC0001

**Response to Restriction Requirement**

Assistant Commissioner for Patents  
Washington, DC 20231

Sir:

In response to the Office Action dated November 26, 1996, applicant hereby elects to prosecute the invention of Restriction Group I, drawn to a microfabricated device and represented by claims 1-16. With regard to the request by the examiner that a single species of generic claim 2 be elected, applicant hereby elects the species of claims 10-11, directed to polynucleotides fixed by attachment of a terminal primary amine derivative to glass. These elections are made without prejudice to or disclaimer of the other claims or inventions disclosed in the application. Applicant may, or may not, choose to pursue non-elected claims in future applications. The elections are made without traverse.

Also enclosed herewith is a petition for a three-month extension of time, along with a check providing the fee for such extension. It is not believed that any additional fees are required for the filing of the enclosed documents. The Assistant Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment to our Deposit Account No. 22-0365. If additional extensions of time are necessary to prevent abandonment of this application, then such additional extensions of time are hereby petitioned under 37 C.F.R.

§ 1.136(a), and any fees required therefor may be charged to our Deposit Account No. 22-0365. A duplicate copy of this Response is enclosed.

Respectfully submitted,

VINSON & ELKINS L.L.P.

*Michael A. Sanzo*

Michael A. Sanzo  
Attorney for Applicant  
Registration No. 36,912

Date: March 18, 1997

1455 Pennsylvania Avenue, N.W.  
Washington, D.C. 20004-1008  
(202) 639-6585

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 029623/0108

In re patent application of

K. Beattie

Group Art Unit: 1645

Serial No. 08/631,751

Examiner: H. Bakalyar

Filed: April 10, 1996

For: MICROFABRICATED, FLOWTHROUGH POROUS APPARATUS FOR  
DISCRETE DETECTION OF BINDING REACTIONS

AMENDMENT AND REQUEST FOR RECONSIDERATION  
UNDER 37 C.F.R. § 1.116

Assistant Commissioner of Patents  
Washington, D.C. 20231  
BOX AF

Sir:

This is a response to the Office Action mailed February 18, 1998, in the above-identified application. A response is due on June 18, 1998, by virtue of the attached Petition for Extension of Time and payment of the required fees. Please charge the requisite fees to Deposit Account No. 19-0741. Please amend the application as follows:

IN THE CLAIMS:

Please cancel claims 12 and 17-58 without prejudice or disclaimer, and add the following claims:

--59. A device for binding a target molecule, comprising:

a substrate having oppositely facing first and second major surfaces;

a multiplicity of discrete channels extending through said substrate from said first major surface to said second major surface;

a first binding reagent immobilized in a first group of said channels, and

a second binding reagent immobilized in a second group of said channels.

60. A device according to claim 59, wherein said first and second binding reagents differ from one another.

61. A device according to claim 59, wherein said first and second binding reagents bind different target molecules.

62. A device according to claim 60, comprising discrete channels having diameters of from about 0.033 micrometers to about 10 micrometers.

63. A device according to claim 60, comprising discrete channels having cross sectional areas of between about  $8.5 \times 10^{-4} \mu\text{m}^2$  to about  $80 \mu\text{m}^2$ .

64. A device according to claim 60, comprising a substrate between about  $100 \mu\text{m}$  to about  $1000 \mu\text{m}$  thick.

65. A device according to claim 60, comprising channels having an inner surface area of between about  $10 \mu\text{m}^2$  and about  $3 \times 10^4 \mu\text{m}^2$ .

66. A device according to claim 60, wherein said groups of channels have areas of between about  $20 \mu\text{m}^2$  to about  $3 \times 10^6 \mu\text{m}^2$ .

67. A device according to claim 60, wherein there are between 400 and 4400 of said groups of discrete channels per  $\text{cm}^2$  of cross-sectional area of the substrate.

68. A device according to claim 60, wherein the inner surface area of the channels in a group of channels is from about 100 to about 1000 times the cross sectional area of the group of channels.

69. A device according to claims 59, 60, 63, 65, 67, or 68, wherein said substrate is fabricated from glass or silicon.

70. A device according to claim 69, comprising a substrate made of nanochannel glass.

71. A device according to claim 69, comprising a substrate made of oriented array microporous silicon.

72. A device according to claims 59, 60, 63, 65, 67 or 68, wherein said binding reagents are effective for carrying out binding reactions selected from the group consisting of binding reactions involving small molecules, macromolecules, particles and cellular systems.

73. A device according to claim 72, wherein said binding reagents are effective for carrying out an analytical task selected from the group consisting of sequence analysis by hybridization, analysis of patterns of gene expression by hybridization of mRNA or cDNA to gene-specific probes, immunochemical analysis of protein mixtures, epitope mapping, assay of receptor-ligand interactions and profiling of cellular populations involving binding of cell surface molecules to specific ligands or receptors.

74. A device according to claim 73, wherein said binding reagents are selected from the group consisting of DNA, proteins and ligands.

75. A device according to claim 74, wherein said binding reagents are oligonucleotide probes.

76. A device according to claim 75, wherein the oligonucleotide probes are attached to channel surfaces via a

primary amine group incorporated into the probes prior to immobilization.

77. A device according to claim 76, wherein said probes are attached to said channel surfaces via a terminal primary amine derivative of said polynucleotide and said glass substrate is derivatized with epoxysilane.

78. A device for binding a target molecule, comprising:  
a substrate having oppositely facing first and second major surfaces;

a multiplicity of discrete channels extending through said substrate from said first major surface to said second major surface;

a first binding reagent immobilized in a first group of said channels, and

a second binding reagent immobilized in a second group of said channels,

further comprising a rigid support, wherein said rigid support is integral to said substrate, or is bonded to said substrate.

79. A device according to claim 78 wherein said support is integral to said substrate.

80. A device according to claim 78, wherein said support is bonded to said substrate.

81. A device according to claim 78, wherein said rigid support comprises wells for delivering fluids to subsets of channels of said substrate.

82. A device according to claim 78, comprising discrete channels having cross sectional areas of between about  $8.5 \times 10^{-4} \mu\text{m}^2$  to about  $80 \mu\text{m}^2$ .

83. A device according to claim 78, comprising channels having an inner surface area of between about  $10 \mu\text{m}^2$  and about  $3 \times 10^4 \mu\text{m}^2$ .

84. A device according to claim 78, wherein said groups of channels have areas of between about  $20 \mu\text{m}^2$  to about  $3 \times 10^6 \mu\text{m}^2$ .

85. A device according to claim 78, wherein there are between 400 and 4400 of said discrete channels per  $\text{cm}^2$  of cross-sectional area of the substrate.

86. A device according to claim 78, wherein the inner surface area of the channels in a group of channels is from about 100 to about 1000 times the cross sectional area of the group of channels.

87. A device according to claims 78, 83, or 86, comprising a substrate fabricated from glass or silicon.

88. A device according to claim 87, comprising a substrate made of nanochannel glass.

89. A device according to claim 87, comprising a substrate made of oriented array microporous silicon.

90. A device according to claims 78, 83, or 86, wherein said binding reagents are effective for carrying out binding reactions selected from the group consisting of binding reactions involving small molecules, macromolecules, particles and cellular systems.

91. A device according to claim 90, wherein said binding reagents are effective for carrying out an analytical task selected from the group consisting of sequence analysis by hybridization, analysis of patterns of gene expression by



hybridization of mRNA or cDNA to gene-specific probes, immunochemical analysis of protein mixtures, epitope mapping, assay of receptor-ligand interactions and profiling of cellular populations involving binding of cell surface molecules to specific ligands or receptors.

92. A device according to claim 91, wherein said binding reagents are selected from the group consisting of DNA, proteins and ligands.

93. A device according to claim 92, wherein said binding reagents are oligonucleotide probes.

94. A device according to claim 93, wherein the oligonucleotide probes are attached to channel surfaces via a primary amine group incorporated into the probes prior to immobilization.

95. A device according to claim 94, wherein said probes are attached to said channel surfaces via a terminal primary amine derivative of said polynucleotide and said glass substrate is derivatized with epoxysilane.

96. A device according to claims 59 or 78, comprising discrete channels having diameters of from about 0.45 micrometers to about 10 micrometers.--

**REMARKS**

Applicant thanks Examiner Bakalyar and Primary Examiner Duffy for the courtesies extended during personal interviews with applicant's representatives on May 8 and 13, 1998. The claim amendments presented above, and the analysis set forth below reflect the substance of the discussions at those interviews.

Prior to submission of the amendments presented above, claims 12 and 17-58 were pending in the application. Claims 12

and 17-20 had been withdrawn from consideration. If the amendments presented above are entered, claims 12 and 17-58 will be canceled and new claims 59-96, including independent claims 59 and 78, will be added to recite more clearly that which applicant regards as his invention.

It is respectfully submitted that the amendments presented herein follow the format discussed with the Examiner in the interviews, and place the claims in condition for allowance. Moreover, the amended claims raise no new issues, and would not require any further search or consideration. Entry pursuant to 37 CFR § 1.116 and favorable reconsideration are respectfully requested.

The cancellation of claims is made herein without prejudice or disclaimer of the subject matter recited therein, and applicant expressly reserves all rights to such subject matter. No new matter is introduced by these amendments. Claims 59-96, including independent claims 59 and 78, thus will be pending for reexamination and reconsideration, which are respectfully requested in view of the foregoing amendments and following remarks.

In the February 18, 1998, Office Action, claims 21-39 and 41-58 were rejected under 35 USC § 112, first paragraph, for lack of written description. Claims 21-58 were rejected under § 112, second paragraph, as indefinite. Claims 36-38, 47-48, and 57-58 were rejected under § 102(b) as anticipated by Saiki et al. ("Saiki") and under § 103(a) as obvious over Pirrung et al. ("Pirrung") in view of Tonucci et al. ("Tonucci") and Guirguis, further in view of "known facts" and Parham et al. ("Parham"). Claims 1-11 and 13-16 were rejected under § 103(a) as obvious over Beattie et al. ("Beattie") and Southern et al. ("Southern") in view of Tonucci and Guirguis. The specific grounds for rejection, and applicant's response thereto, are set out in detail below.

**Support for Amendments**

The new claims point out more clearly and distinctly that which applicant claims as his invention. Each new claim is supported by the specification. Support for certain terms recited in the claims was discussed in the interview, and is reiterated here for the Examiner's convenience.

**"Channels"**

The term "channels" finds support throughout the specification, as shown by the following exemplary statements.

Page 1, line 18 et seq.: ("[t]he present invention provides a novel flow-through genosensor, in which nucleic acid recognition elements are immobilized within densely packed pores or channels").

Example 1, page 14, lines 10-14: (nanochannel glass ("NCG") wafers contain "a regular geometric array of parallel holes or channels as small as 33 nm in diameter or as large as several micrometers in diameter [that]. . . can possess packing densities in excess of  $3 \times 10^7$  channels per square centimeter").

Page 15, lines 3-5 and 8-9: (two typical channel diameters are 450 and 300 nm, respectively.)

Example 3, page 18, lines 19 - 27: (porous silicon can be fabricated with "dense oriented arrays of pores" having a wide range of diameters or that are rectangular.)

**"Binding reagents immobilized in . . . channels"**

The term "binding reagents immobilized in . . . channels" finds support throughout the specification, as shown by the following exemplary statements.

Subparagraph "(m)" at page 9, line 15 et seq.: ("A microfabricated device, . . . comprising: (1) a substrate . . . (2) an array of discrete and isolated regions arranged across a surface of said substrate and extending there through to a second surface of said substrate, thereby forming pores in said substrate; (3) substantially homogeneous samples of a

predetermined set of biomolecules . . . being fixed in one or more of said regions, such that one or more of said molecules is capable of binding with a molecular species passing there through.")

Page 13, lines 7-9: (a "porous wafer containing 0.1-10 micron diameter channels comprising the bonding region for biomolecules fixed therein.")

Page 15, line 7 et seq. (describes "DNA binding capacity" and compares increased binding of probes to insides of channels with amounts that can be bound to a flat surface.  $10^8$  probes can be bound to a 50 micrometer square area of flat surface, whereas  $10^{10}$  to  $10^{11}$  probes can be bound within a 50 micrometer cube of a porous silicon wafer. Similarly, whereas "at least  $10^7$ " longer, plasmid molecules can be attached per square mm of flat glass,  $10^9$ - $10^{10}$  plasmid molecules can be immobilized per square mm of cross section of a porous wafer.

Page 1, line 28 et seq.: ("vastly increased surface area . . . per cross sectional area" for immobilizing binding reagents.)

Page 16, line 4: ("The DNA sample is flowed into the porous regions of the chip and incubated" indicating that hybridization of target to probe occurs in the channels of the chip, where the probes are immobilized.)

Page 20, line 5-7: ("The epoxysilane-amine linkage procedure described in EXAMPLE 4 is then carried out to covalently attach amine-containing biopolymer species to the walls of the pores.")

Page 32, lines 19-20: ("The pores of the wafer are activated to bind amine-derivatized polynucleotides by reaction with epoxysilane, as described in EXAMPLE 4.")

#### **"Binding reagent"**

The term "binding reagent" finds support throughout the specification, as shown by the following exemplary statements.

Title of the application: "\* \* Apparatus for Discrete Detection of Binding Reactions.")

Page 2, lines 12-13: ("the present invention provides . . . an improved apparatus and method - for simultaneous conduct of . . . binding reactions on a substrate." Binding reactions inherently require binding reagents, and a wide variety of reagents used for binding reactions are disclosed in the specification, for example at page 4, line 25 through page 5 line 3 and at page 12, line 25 through page 13 line 2).

#### **Dimensions and densities of wafers and channels**

The dimensions and areas recited in the claims are supported throughout the specification, which describes the dimensions of wafers and channels, channel spacing, and the arrangement of channels in substrates. Cross sectional surface areas are dictated by diameters, and can be calculated from the diameters by simple geometrical formulae. Similarly, surface areas inside channels may be calculated using the known channel diameters and wafer thicknesses. The percentage of substrate surface area occupied by channels can be calculated using the dimensions of the channel and the distance between the channels.

Page 14, line 10: (The channels may have diameters as small as 33 nm up to "several micrometers.")

Page 18, line 3: (Channels in porous silicon wafers can have diameters "from 2 nm to several micrometers.")

Page 19, line 15: (Channels typically have diameters of 0.2 micrometers.)

Page 13, lines 7-8: (Porous wafers "containing 0.1 to 10 micrometer diameter channels." Cross-sectional areas of channels can be calculated directly from diameters.)

Page 14, lines 28-30: (wafers can be 0.1 to 10 micrometers thick.)

Page 15, lines 11: (450 nm diameters of channels, 750 nm spacing between channels - provides cross-sectional area that is about 28% channels and about 72% solid substrate. Ratios of

(channel surface area): (cross sectional area of the substrate) can be calculated from channel diameters, substrate thickness, and the diameter of the group of channels.)

Page 25, lines 8-20: (This section discusses cross sectional areas of groups of channels in which DNAs are immobilized, and states that about  $10^8$  oligonucleotide molecules can be immobilized in a  $50\mu\text{m} \times 50\mu\text{m}$  area of flat surface, but that  $10^{10}$  to  $10^{11}$  molecules can be immobilized in  $50\mu\text{m}$  cube of porous silicon. Similarly, at least  $10^7$  molecules of plasmid pBR322 can be immobilized per  $\text{mm}^2$  of flat glass surface,  $10^9$  to  $10^{10}$  molecules of pBR322 can be immobilized per  $\text{mm}^2$  of cross sectional area of nanoporous substrates.

#### **Types of binding reactions**

See, *inter alia*, page 4, line 25 through page 5 line 3; page 12, line 25 through page 13 line 2.

#### **Groups of channels**

Claim recitations relating to groups of channels with immobilized binding reagents are supported generally throughout the specification. See, for example, page 15, line 6-11. In addition, the specification illustrates groups of channels defined by immobilization of binding reagents in discrete and isolated regions, such as those defined by the wells in the manifold depicted in Figure 1.

#### **Discrete channels**

Claim recitations to "discrete channels" are generally supported throughout the specification. See also Figures 1-4 and Example 1, and the discussion set forth below.

**The Term "discrete and isolated"**

*not in claims*

As discussed during the interviews, the specification of the instant application applies the term "discrete and isolated" to several different types of "regions" of the claimed devices.

For example, one such "region" is the pore or channel that extends through a substrate. Another example is the region defined by the group of channels where a given binding reagent is immobilized. This second type of "region" is defined, therefore, by the presence of the binding reagent. Methods of demarcating a region in this fashion may use, for example, a spotter, such as an ink-jet dispenser, that determines where each binding reagent is immobilized on the substrate. Similarly, a manifold can determine where binding reagents contact and are immobilized in a substrate. The present application states that a suitable manifold may, for example, be bonded to a substrate or may be integral.

In addition, page 15, lines 7-11, of the specification states that "separated clusters of channels" may be "formed during the [substrate] fabrication process." It will be understood that such separated clusters are structural features that also are "discrete and isolated" regions. It also will be understood that a "discrete and isolated" region can be defined by the sample wells in a manifold that determines where samples contact a substrate.

In sum, "discrete and isolated" regions may be formed in several ways within the context of the claimed invention. It should be noted that substrates of the claimed invention have discrete channels extending through the substrate. These discrete channels are only one type of "discrete and isolated region" set forth in the disclosure. The claims also recite use of first and second binding reagents that are immobilized in first and second groups of the discrete channels. A group of channels defined by the presence of a binding reagent is a second type of discrete and isolated region. Such channel groups can be defined, for example, by "separated clusters" of channels that are fabricated in the substrate. Other ways to define such groups of channels include use of a manifold for distributing binding reagents or samples to discrete and isolated regions of

the substrate. The skilled artisan readily will appreciate other ways in which such regions can be formed.

**Rejections under 35 USC § 112, first paragraph**

Claims 21-39 and 41-58 are rejected under 35 USC § 112, first paragraph, for lack of written description. Specifically, the Action states that the specification fails to provide adequate written description for: (i) the "discrete or isolated channels" in claims 21 and 23; (ii) the "concept" of a single well abutting a plurality of channels as recited in claims 36, 38, and 39; and (iii) the array element recited in claim 39. Applicant respectfully traverses.

Each of these terms or "concepts" is fully supported by the specification, as detailed above. With respect to the rejections of the elements recited in claims 36, 38, and 39, applicant respectfully submits that these rejections are rendered moot in light of the new claims presented herein, which do not recite any of the offending terms.

**Rejections under 35 USC § 112, second paragraph**

Claims 21-58 are rejected under 35 USC § 112, second paragraph, for indefiniteness. Specifically, the Action states that the recitation "set of channels" lacks antecedent basis and that the "structural basis" for the term "adapted to receive" is "unclear." Applicant respectfully traverses the rejection because the meaning of each of the allegedly indefinite recitations is clear to one skilled in the art. Nevertheless, these rejections are rendered moot in light of the new claims presented herein, which do not recite either of the offending terms.

**Rejections under 35 USC § 102**

Claims 36-38, 47-48, and 57-58 are rejected under § 102(b) as anticipated by Saiki et al. ("Saiki"). Applicant respectfully traverses the rejection.



For a prior art reference to be anticipatory, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990). Saiki fails to show every element of the instantly claimed invention and, accordingly, cannot anticipate that invention.

In the instantly claimed invention, binding reagents are immobilized in discrete channels that extend through a substrate. By contrast, Saiki describes methods for immobilizing oligonucleotides on membranes that either are fibrous or porous. Fibrous membranes are made of amorphously distributed fibers and provide an irregular, amorphous passage for liquids that is interconnected throughout the membrane. Reagents bind to the fibers of these membranes. Porous membranes contain relatively few pores distributed in an impermeable material. The membranes generally are thin with very small pores that do not appreciably contribute to overall surface area. Reagents thus bind essentially to the upper or lower surfaces of porous membranes. Accordingly, one skilled in the art would appreciate that membranes do not contain discrete channels that extend through a substrate, as required in the instantly claimed invention.

In sum, Saiki fails to describe devices containing discrete channels that extend through a substrate moiety. Accordingly, Saiki does not describe every elements of the claimed invention. Applicant therefore respectfully requests that the rejection be reconsidered and withdrawn.

**Rejections under 35 USC § 103**

Claims 36-38, 47-48, and 57-58 are rejected under USC § 103(a), as obvious over Pirrung in view of Tonucci and Guirguis, further in view of "known facts" and Parham. Claims 1-11 and 13-16 also are rejected under § 103(a) as obvious over Beattie and Southern in view of Tonucci and Guirguis. Applicant addresses each of these rejections in turn.

Pirrung in view of Tonucci and Guirguis, further in view of "known facts" and Parham

The Action states that Pirrung teaches synthesis of oligonucleotide arrays, that Tonucci teaches nanochannel glass wafers, that Guirguis teaches use of microporous membranes in binding assays, and that applicant's specification admits that certain methods for linking DNA to glass are well known. The Action alleges that it would have been obvious, therefore, to use the wafers taught by Tonucci to bind the oligonucleotide arrays taught by Pirrung in assays of the type taught by Guirguis. Applicant respectfully traverses.

In combining references, the PTO is obliged to show by reference to specific evidence in the cited references that there was (i) a suggestion to make the combination and (ii) a reasonable expectation that the combination will succeed. *Both the suggestion and reasonable expectation must be found within the prior art*, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicant submits that not only is there no proper motivation to combine the references, but that for the reasons set forth below one of ordinary skill in the art would not have had a reasonable expectation that the combination would succeed. Accordingly, no *prima facie* case of obviousness exists.

First, the Action alleges that each individual element of the claimed invention is taught or described in a separate reference, and asserts that the combination of these elements would have been obvious because the supposed properties of that combination are "well known advantages of filtration-based specific binding assays."

However, it is the PTO's burden to point to specific evidence in the cited references that would have provided the motivation for one of ordinary skill in the art to combine the references. Applicant respectfully submits that the only motivation to combine the cited references is provided by a hindsight

reconstruction of the prior art in view of the teachings of the applicant's specification. Such a hindsight reconstruction is, of course, quite improper. See *Grain Processing Corp. v. American Maize-Products Corp.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988).

Second, even if a proper motivation exists to combine the references, one of ordinary skill in the art would not have had a reasonable expectation that the combination would succeed. In particular, the methods described by Pirrung are singularly unsuited for applying to a substrate having a multiplicity of discrete channels that extend through the substrate.

Rather, Pirrung discloses a method for synthesizing peptides or oligonucleotides in spatially distinct locations on a surface. Light is used to activate specific areas on the surface for each of series of monomer addition reactions, and requires careful control of illumination of the surface. Pirrung repeatedly emphasizes that a flat surface is required for successful application of the method:

[t]he substrate is preferably flat . . .  
.[but] may contain raised or depressed  
regions on which synthesis takes place  
[i.e., the flat regions on which synthesis  
takes place may be raised or depressed  
relative to the overall substrate  
surface].

See column 11, lines 14-52.

The reason for the requirement of an essentially flat surface is to ensure that the surface can be evenly illuminated, thereby permitting the required level of consistency to the photoactivated synthesis reactions. One of ordinary skill in the art would recognize the significant difficulties of achieving the necessary uniform illumination inside a multiplicity of channels extending through a substrate.

Moreover, the Examiner correctly notes that Pirrung teaches that a curved substrate surface can be used in the photoactivation methods, but notes that this is "more difficult"

than using a flat surface. A curved surface is a far cry, however, from a substrate that has channels extending through the substrate. If Pirrung acknowledges that use of a surface that merely is "curved" is "more difficult," one of ordinary skill in the art would have recognized that use of a substrate with channels extending through the substrate would be much, much "more difficult." Accordingly, one skilled in the art would not have had a reasonable expectation of success in using Tonucci's nanochannel glass as a substrate for the assays described by Pirrung.

In sum, applicant respectfully submits that one of ordinary skill in the art would not have been motivated to combine the cited references, and would not have had a reasonable expectation that the combination would work for its intended purpose. The secondary references cannot remedy this deficiency and, accordingly, applicant respectfully requests that the rejection be withdrawn.

**Beattie and Southern in view of Tonucci and Guirguis.**

The Action states that Beattie teaches genosensors where DNA probes are attached to a glass surface, and that Southern teaches genosensors that employ multiple wells aligned with a plurality of channels. The Action admits, however, that neither Beattie nor Southern teaches use of a substrate material that contains channels extending through the substrate. This deficiency allegedly is remedied by Tonucci's teaching of nanochannel glass wafers. Guirguis is cited as teaching the advantages of using microporous membranes in specific binding assays, in particular their high binding capacity. Accordingly, the Action alleges that it would have been obvious to use the wafer taught by Tonucci as a substrate for the genosensors described by Beattie or Southern "because of the expectation of successfully making a high density, highly-sensitive genosensor device." Applicant respectfully traverses.

Serial No. 08/631,751

This rejection employs essentially the same rationale as the rejection over Pirrung in view of Tonucci and Guirguis. The instant rejection is fatally flawed, however, for essentially the same reasons as set forth above for the earlier rejection. Thus, the Action fails to point to evidence in any of the cited references that would have motivated the routineer to combine those references. Applicant submits once more that the only motivation to combine the cited references is provided by a proscribed hindsight reconstruction of the prior art in view of the teachings of the applicant's specification. Accordingly, applicant respectfully submits that the rejection is improper and should be withdrawn.

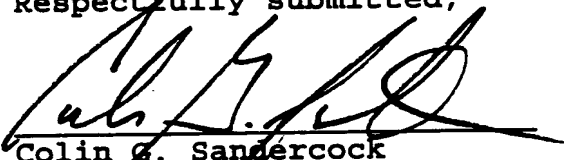
**CONCLUSION**

In view of the foregoing, it is respectfully urged that the present claims are in condition for allowance. An early notice to this effect is earnestly solicited. Should there be any questions regarding this application, the Examiner is invited to contact the undersigned at the number shown below.

If any additional extension(s) of time are required for the filing of this paper, applicant expressly petitions for such extension(s) and authorize the Commissioner to charge any deficiency to Deposit Account 19-0741.

Respectfully submitted,

5/28/98  
Date

  
Colin G. Sandercock  
Reg. No. 31,298

FOLEY & LARDNER  
Suite 500, 3000 K Street, N.W.  
Washington, D.C. 20007-5109  
(202) 672-5300

# PATENT

I hereby certify that on the date specified below, this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, 2011 Jefferson Davis Highway, Washington, DC 20231.

Date November 12, 1997 Angela S. Long  
Angela S. Long

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**Applicant** : **Kenneth L. Beattie**  
**Application No.** : **08/631,751**  
**Filed** : **April 11, 1996**  
**For** : **MICROFABRICATED, FLOWTHROUGH POROUS  
 APPARATUS FOR DISCRETE DETECTION OF BINDING  
 REACTIONS**

**Examiner** : Heather Bakalyar, Ph.D.

Art Unit : 1818

**Docket No. : 390036.407C1**

**Date** : **November 12, 1997**

**Assistant Commissioner for Patents**  
2011 Jefferson Davis Highway  
Washington, DC 20231

**AMENDMENT**

Sir:

In response to the Office Action dated May 13, 1997, please extend the period of time for response three months, to expire on November 13, 1997. Enclosed are a Petition for an Extension of Time and the requisite fee. Please amend the application as follows:

**In the Specification:**

On page 13, line 14, please delete "Delrin" and insert therefor --DELRIN--.

On page 13, line 20, please delete "Delrin" and insert therefor --DELFIN--.

On page 20, line 15, please delete "Drierite" and insert therefor --DRIERITE (anhydrous calcium sulfate)--.

On page 20, line 29, please delete "Microlab" and insert therefor --MICROLAB--.

In the Claims:

Please cancel claims 1-11 and 13-16.

Please add claims 21-58:

-- 21.           A binding reaction apparatus for receiving a liquid sample, comprising:  
                  a first layer having a plurality of discrete channels, each extending in a substantially first orientation through the first layer, and  
                  a second layer having a multiplicity of wells, each extending in a substantially second orientation through the second layer;  
                  wherein the first and second layers are bonded together such that the first and second orientations are the same and each well of the second layer abuts a corresponding set of the channels of the first layer;  
                  wherein the wells of the second layer are operable to receive the liquid sample;  
and  
                  wherein the channels are operable to allow the liquid sample to flow therethrough.

22.     The apparatus of claim 21, wherein the channels of the first layer have biomolecules immobilized therein.

23.     A binding reaction apparatus for receiving a liquid sample, comprising:  
                  a first layer having a plurality of channels, each extending in a substantially first orientation through the first layer, and

a second layer having a multiplicity of wells, each extending in a substantially second orientation through the second layer;

wherein the first and second layers are bonded together such that the first and second orientations are the same and each well of the second layer abuts a corresponding set of the channels of the first layer;

wherein the channels of the first layer have biomolecules immobilized therein;

wherein the wells of the second layer are operable to receive the liquid sample;

and

wherein the channels are operable to allow the liquid sample to flow therethrough.

24. The apparatus of either of claims 21 or 23, wherein the first layer is glass or silicon.

25. The apparatus of claim 24, wherein each channel has a diameter of from about 0.1  $\mu\text{m}$  to 10  $\mu\text{m}$ .

26. The apparatus of claim 24, wherein each set of channels has a width of from about 5  $\mu\text{m}$  to about 2000  $\mu\text{m}$ .

27. The apparatus of claim 24, wherein the apparatus comprises from about 400 to about 4400 sets of channels/ $\text{cm}^2$ , wherein each set of channels has a width of from about 5  $\mu\text{m}$  to about 2000  $\mu\text{m}$ , and wherein adjacent sets of channels are spaced apart from about 0.1 to 10 times their width.

28. The apparatus of either of claims 21 or 23, wherein the first layer includes the channels distributed uniformly therein.

29. The apparatus of either of claims 21 or 23, wherein the second layer consists essentially of a polymeric material.



30. The apparatus of either of claims 21 or 23, wherein the first and second layers consist essentially of a silicon material.

31. The apparatus of either of claims 22 or 23, wherein the immobilized biomolecules include DNA molecules, RNA molecules or proteins.

32. The apparatus of claim 31, wherein the DNA molecules are oligonucleotides, amplified DNA fragments or clone DNA.

33. The apparatus of either of claims 21 or 23, wherein the liquid sample comprises sample biomolecules.

34. The apparatus of claim 33, wherein the sample biomolecules are labeled.

35. The apparatus of claim 34, wherein the label is a fluorescent label, a radioactive label, or a chemiluminescent label.

36. A binding reaction apparatus adapted to receive a liquid sample, comprising a substrate having a plurality of wells, each well abutting and aligning with a corresponding plurality of channels; the wells being operable to receive a liquid sample; and the channels being operable to allow the liquid sample to flow therethrough.

37. The apparatus of claim 36, wherein the channels have biomolecules immobilized therein.

38. A binding reaction apparatus adapted to receive a liquid sample, comprising a substrate having a plurality of wells, each well abutting and aligning with a corresponding plurality of channels; the wells being operable to receive a liquid sample; the

channels having biomolecules immobilized therein and being operable to allow the liquid sample to flow therethrough.

39. A binding reaction apparatus adapted to receive a liquid sample, comprising a substrate having a plurality of array elements; wherein each array element includes a plurality of channels, the channels being arranged in discrete and isolated regions, the channels having biomolecules immobilized therein, the channels being operable to receive a liquid sample and being operable to allow the liquid sample to flow therethrough.

40. A binding reaction apparatus adapted to receive a sample, comprising a substrate having a plurality of discrete and isolated channels extending substantially straight therethrough, the channels having biomolecules immobilized therein and being operable to allow the sample to flow therethrough.

41. The apparatus of claim 40, wherein the channels are arranged in an array, each array element including a corresponding set of the channels.

42. The apparatus of any one of claims 36, 38, 39, or 40, wherein the substrate is glass or silicon.

43. The apparatus of claim 42, wherein each channel has a diameter of from about 0.1  $\mu\text{m}$  to 10  $\mu\text{m}$ .

44. The apparatus of claim 42, wherein each set of channels has a width of from about 5  $\mu\text{m}$  to about 2000  $\mu\text{m}$ .

45. The apparatus of claim 42, wherein the apparatus comprises from about 400 to about 4400 sets of channels/ $\text{cm}^2$ , wherein each set of channels has a width of from about 5  $\mu\text{m}$  to about 2000  $\mu\text{m}$ , and wherein adjacent sets of channels are spaced apart from about 0.1 to 10 times their width.

46. The apparatus of claim 42, wherein the channels are substantially rectangular.

47. The apparatus of any one of claims 37, 38, 39, or 40, wherein the immobilized biomolecules include DNA molecules, RNA molecules or proteins.

48. The apparatus of claim 47, wherein the DNA molecules are oligonucleotides, amplified DNA fragments, or clone DNA.

49. The apparatus of any one of claims 36, 38, 39, or 40, wherein the liquid sample comprises sample biomolecules.

50. The apparatus of claim 49, wherein the sample biomolecules are labeled.

51. The apparatus of claim 50, wherein the label is a fluorescent label, a radioactive label, or a chemiluminescent label.

52. The apparatus of any one of claims 21, 23, 36, 38, 39, or 40, wherein the channels include epoxysilane-derivatized glass channels, and wherein the biomolecules are attached through a primary amine group thereto.

53. The apparatus of any one of claims 21, 23, 36, 38, 39, or 40, wherein the channels include oxidized-silicon channels, and wherein the immobilized biomolecules are attached through a primary amine group thereto.

54. The apparatus of any one of claims 21, 23, 36, 38, 39, or 40, wherein a pressure difference is applied to facilitate the liquid sample to flow therethrough.

55. The apparatus of claim 54, wherein the pressure difference is generated by a vacuum chamber coupled to the apparatus.

56. The apparatus of claim 54, wherein the pressure difference is generated by a pressure chamber coupled to the apparatus.

57. The apparatus of any one of claims 21, 23, 36, 38, 39, or 40, wherein the density of channels is from about  $10^7$  to at least  $3 \times 10^{10}$  channels per  $\text{cm}^2$ .

58. The apparatus of any one of claims 21, 23, 36, 38, 39, or 40, wherein the binding reaction is nucleic acid hybridization or protein-protein binding. --

#### REMARKS

Applicant respectfully requests reconsideration of the application in view of the above amendments and following remarks. Claims 21-58 are now in this case. Claims 1-11 and 13-16 have been canceled without prejudice to the filing of any continuation, continuation-in-part or divisional application. Claims 21-58 have been added to replace the canceled claims in order to more clearly define the invention, without limiting the scope of the claims. These added claims draw support from throughout the specification and the original claims.

#### **Objections to the Specification**

The Examiner objected to the disclosure because of the use of certain trademarked names without sufficient indication of the trademark.

Applicants have responded to this objection by correcting these informalities.

#### **Claim Rejections under § 112 (2)**

The Examiner rejected Claims 1-11 and 13-16 under 35 U.S.C. §112(2) for being indefinite.

Applicant respectfully traverses this rejection. Applicant respectfully submits that the claims presented for examination herein comply with the requirements of Section 112, second paragraph. As noted above, the present claims have been entered to clarify recitation of the claimed subject matter without, however, limiting its scope. Accordingly, applicant requests that the Examiner withdraw the rejections.

#### **Claim Rejections under § 102(b)**

The Examiner rejected Claims 1-2 and 14-15 in the belief that these claims are anticipated by Saiki et al.

Applicant respectfully traverses this rejection. Applicant submits that this rejection does not apply to the currently pending claims. In particular, the membrane of Saiki et al. is a nylon filter that does not have a plurality of discrete, aligned channels. Discrete, aligned channels generally inhibit lateral diffusion of a liquid therein and any of its constituents. Lateral diffusion is an undesirable characteristic, especially when different biomolecules are being immobilized or when different constituents are being contacted with the immobilized biomolecules. In contrast, a nylon filter is unstructured and readily allows lateral diffusion. Furthermore, unlike certain aspects of the present invention, the membrane disclosed by Saiki et al. does not have a multiplicity of wells that abut and align with a plurality of channels. Thus, in contrast to the instant apparatus, the membrane of Saiki et al. has no channels and no wells. Therefore, applicant requests that the Examiner withdraw this rejection.

#### **Claim Rejections under § 103(a)**

(1) The Examiner rejected Claims 1-11 and 13-16 in the belief that these claims are obvious over Pirrung et al. in view of Tonucci et al. and Guirguis. More specifically, the Examiner is of the opinion that Pirrung et al. teach a substrate for synthesizing oligonucleotide arrays in which the synthesis area may be separated by *e.g.* wells or raised regions; that Tonucci et al. teach nanochannel filters; and that Guirguis teaches advantages of using microporous membranes in immunoassays. The Examiner then concludes that it would have been obvious to use the wafers taught by Tonucci et al. as the

substrate for the arrays of Pirrung et al. in view of the advantages of membranes suggested by Guirguis.

Applicant respectfully traverses this rejection. Applicant submits that a person of ordinary skill in the art would not have been motivated to combine the disclosures in any way that could have rendered the claimed invention obvious, as the Examiner suggests. Applicant furthermore respectfully submits that, even if the cited references were adequately "suggestive," a person of ordinary skill would not have had a reasonable expectation of success from any combination of the references. Indeed, as explained below, applicant respectfully submits that the apparatus resulting from the combination of the cited art appears inoperable. As such, the combination relied upon in the rejection teaches away from the claimed invention.

The Pirrung et al. patent is directed toward synthesis of polymers, particularly peptides and oligonucleotides, using photo-activation chemistries and photolithographic techniques. The polymers in the Pirrung et al. patent are synthesized in discrete areas on an essentially flat surface that allows the areas of synthesis to be evenly exposed to a light beam. Thus, the illustrations and the examples in this patent, as well as a reading of the specification as a whole, relate virtually solely to flat substrates. Furthermore, according to Pirrung et al., deviations from a flat surface, such as "wells, raised region, etched trenches, or the like" (col. 7, lines 54) serve to "*physically separate synthesis regions*" on otherwise flat surfaces (col. 7, line 52-53; emphasis added). For these reasons, applicant submits that a person of ordinary skill in the art would not have been motivated to use a porous or "flow through" substrate in the method of Pirrung et al. Therefore, on this basis alone, applicant respectfully requests that the rejection be withdrawn.

In addition, applicant submits that one of skill in the art would not have a likely expectation of success in using the claimed apparatus as the substrate for the biomolecular arrays of Pirrung et al. In particular, the apparatus of the instant invention is unlikely to be useful for the photolithography methods taught by Pirrung et al. as the porous channels are not readily amenable to the masking technology. In this regard, photolithography requires that the illuminated areas receive an even exposure to light. An apparatus with channels transverse to the light source cannot be evenly illuminated.

Applicant submits that these deficiencies of Pirrung et al. are not cured by the addition of the Tonucci et al. reference. In this regard, the thrust of the Tonucci et al. patent is towards fabrication of a filtering device made of glass in order to size separate particles or gases. Thus, these filters are designed and disclosed solely for separation purposes. Tonucci et al. do not teach or suggest the use of nanochannel filters for the attachment of biomolecules to the channels or for any type of binding reaction between molecules. Applicant submits that the substitution of the nanoporous glass filters of Tonucci et al. as the substrate for the synthesis substrate of Pirrung et al. do not suggest the present invention. Furthermore, inasmuch as Pirrung et al. desire even illumination of the substrate surface, one of ordinary skill would not likely consider using porous substrates.

Moreover, applicant doubts whether one skilled in the art would look to Tonucci et al. for any guidance, given the different art field to which Tonucci et al. is directed. The Examiner's attention is particularly directed to the distinct classifications of the instant application and the Tonucci et al. patent.

The further addition of the Guirguis patent does not correct the major deficiencies noted above. The Guirguis patent discusses enzyme immunofiltration assays in very general terms. A careful reading of this discussion reveals that the procedure and physical setup appear very different from the present invention. For example, in contrast to the present invention, antibody is absorbed onto polystyrene particles, which are non-porous, and then "caught on a filter" (column 3, lines 16-18). Thus, the antibodies (*e.g.*, biomolecules) in Guirguis are not attached to the porous portion of the substrate. Furthermore, the porous portion of the immunofiltration device is merely to enhance fluid flow rate. In contrast, the porous channels of the present invention serve both as attachment sites for biomolecules as well as a means of, and location for, contacting a liquid sample with the biomolecules. Therefore, applicant submits that Guirguis, alone or in combination with the other cited references, do not teach or suggest any aspect of the present invention. Applicant respectfully requests that the Examiner withdraw this rejection.

(2) The Examiner rejected Claims 10-11 in the belief that these claims are obvious over Pirrung et al. in view of Tonucci et al. and Guirguis and in further view of the instant specification and Parham et al.

Applicant respectfully traverses this rejection. The grounds of the rejection are essentially the same as for the rejection over Pirrung et al., Tonucci et al., and Guirguis, except that Parham is additionally cited as teaching a specifically recited immobilization chemistry. Applicant respectfully submits that in view of the deficiencies of the primary references, the additional recitation of a specific immobilization chemistry does not render the claimed invention obvious. Therefore, applicant respectfully requests that the rejection should be withdrawn for the reasons discussed above with respect to the rejection over Pirrung et al., Tonucci et al., and Guirguis.

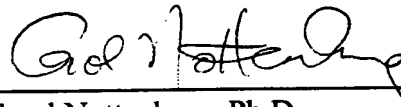
(3) The Examiner rejected Claims 1-11 and 13-16 in the belief that these claims are obvious over Beattie et al. in view of Tonucci et al. and Guirguis. The Examiner cites Beattie et al. for disclosing DNA attachment chemistries, but concedes that the Beattie et al. reference do not teach the instant apparatus. The Examiner appears to rely on the Tonucci et al. reference for teaching the substrate and the Guirguis reference for supplying motivation.

Applicant respectfully traverses this rejection. The grounds of the rejection are essentially the same as for the rejection over Pirrung et al., Tonucci et al., and Guirguis, except that the Beattie et al. reference is additionally cited as disclosing DNA attachment chemistries. Furthermore, the Beattie et al. reference only illustrates attachment to an essentially flat surface. In this regard, applicant draws the Examiner's attention to Figures 2 and 3, which illustrate DNA attachment to a glass surface. As well, the text of the reference makes no suggestion of using a porous substrate, such as claimed in the present invention. Thus, applicant respectfully submits that in view of the deficiencies of the primary references, the additional recitation of attachment chemistries does not render the claimed invention obvious. Therefore, on the basis of the reasons discussed herein and discussed above with respect to the rejection over Pirrung et al., Tonucci et al., and Guirguis, applicant respectfully requests that the rejection be withdrawn.



Applicant believes that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If any issues remain, the Examiner is encouraged to contact the undersigned attorney at 206-622-4900.

Respectfully submitted,  
Kenneth L. Beattie  
SEED and BERRY LLP



---

Carol Nottenburg, Ph.D.  
Registration No. 39,317

CN:asl

Enclosures:

Postcard  
Check No. 48066 for \$2,511  
Form PTO-1083 (+ copy)  
Petition for an Extension of Time (+ 2 copies)

6300 Columbia Center  
701 Fifth Avenue  
Seattle, Washington 98104-7092  
(206) 622-4900  
Fax: (206) 682-6031

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PATENT

I hereby certify that on the date specified below, this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, 2011 Jefferson Davis Highway, Washington, DC 20231.

November 12, 1997  
Date

Angela S. Long  
Angela S. Long

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kenneth L. Beattie  
Application No. : 08/631,751  
Filed : April 11, 1996  
For : MICROFABRICATED, FLOWTHROUGH POROUS  
APPARATUS FOR DISCRETE DETECTION OF BINDING  
REACTIONS

Examiner : Heather Bakalyar, Ph.D.  
Art Unit : 1818  
Docket No. : 390036.407C1  
Date : November 12, 1997

Assistant Commissioner for Patents  
2011 Jefferson Davis Highway  
Washington, DC 20231

PETITION FOR AN EXTENSION OF TIME  
UNDER 37 C.F.R. § 1.136(a)

Sir:

Applicant herewith petitions the Assistant Commissioner of Patents under 37 C.F.R. § 1.136(a) for a three-month extension of time for filing the response to the Examiner's Action dated May 13, 1997, from September 13, 1997 to November 13, 1997. Submitted herewith is a check in the amount of \$2,511, \$950 of which is to cover the cost of the extension.

Any deficiency or overpayment should be charged or credited to Deposit Account No. 19-1090. This petition is being submitted in triplicate.

Respectfully submitted,

Kenneth L. Beattie

SEED and BERRY LLP

Carol Nottenburg  
Carol Nottenburg, Ph.D.  
Registration No. 39,317

CN:asl

Enclosures:

Postcard

Check No. 48066 for \$2,511

Two copies of this Petition

6300 Columbia Center  
701 Fifth Avenue  
Seattle, Washington 98104-7092  
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UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

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Washington, D.C. 20231

08/16 31751

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

- (1) Larry Millstein JG (3) Carol Nottenburg CN  
(2) Larry Tiffany AT (4) \_\_\_\_\_

Date of interview \_\_\_\_\_

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description: \_\_\_\_\_

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed: electrical claims

Identification of prior art discussed: cited

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Discussed 112(2);

Applicant discussed potential clarification of claimed invention.  
Exr advised another reader in response to claim proposed claim  
and it would be withdrawn.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

Unless the paragraphs below have been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

☐ Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action.

HATZ  
Examiner's Signature

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§ 1.133 Interviews.

. . . . .

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office actions as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desirable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the



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Patent and Trademark Office  
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SEPTEMBER 15, 1996

PTAS



\*100216242A\*

VINSON & ELKINS L.L.P.  
MICHAEL A. SANZO  
THE WILLARD OFFICE BUILDING  
1455 PENNSYLVANIA AVE., N.W., SUITE 800  
WASHINGTON, D.C. 20004-1008

UNITED STATES PATENT AND TRADEMARK OFFICE  
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 04/10/1996

REEL/FRAME: 7981/0845  
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

BEATTLE, KENNETH L.

DOC DATE: 01/23/1996

ASSIGNEE:

HOUSTON ADVANCED RESEARCH CENTER  
4800 RESEARCH FOREST DRIVE  
THE WOODLANDS, TEXAS 77381

SERIAL NUMBER: 08631751

PATENT NUMBER:

FILING DATE: 04/10/1996

ISSUE DATE:

TARA WASHINGTON, EXAMINER  
ASSIGNMENT DIVISION  
OFFICE OF PUBLIC RECORDS

06-20-1996

U.S. DEPARTMENT OF COMMERCE

631751

To the Honorable Commissioner of Patents and T.

100216242

Documents or copy thereof.

1. Name of conveying party(ies):

Kenneth L. Beattie

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Houston Advanced Research Center

Internal Address: \_\_\_\_\_

Street Address: 4800 Research Forest DriveCity/State/ZIP: The Woodlands, Texas 77381Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger  
☐ Security Agreement ☐ Change of Name  
☐ Other \_\_\_\_\_

Execution Date: January 23, 1996

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: \_\_\_\_\_

A. Patent Application No.(s)

PCT/US94/12282

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Michael A. Sanzo

Internal Address: \_\_\_\_\_

Street Address: Vinson & Elkins L.L.P.  
The Willard Office Building  
1455 Pennsylvania Avenue, N.W., Suite 800City/State/ZIP: Washington, D.C. 20004-1008

6. Total number of applications and patents involved:

1

7. Total Fee (37 C.F.R. § 3.41) ..... \$ 40.00

- ☐ Enclosed  
☒ Authorized to be charged to deposit account

8. Deposit account number:

22-0365

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Michael A. Sanzo  
 Name of Person Signing

Michael A. Sanzo  
 Signature

April 11, 1996  
 Date

Total number of pages including cover sheet, attachments, and document:

2

Mail documents to be recorded with required cover sheet information to:  
 Commissioner of Patents & Trademarks, Box Assignments  
 Washington, D.C. 20231

FORM6-03.WP5

ASSIGNMENT

As a below-named inventor, I hereby declare that:

My post office address is as stated below under my signature and I am named as an inventor of the inventions or discoveries (herein INVENTIONS) as described in the patent application (herein APPLICATION) identified below. In view of valuable consideration, receipt thereof is hereby acknowledged, I do hereby assign and transfer unto Houston Advanced Research Center, hereinafter "HARC", a not-for-profit corporation of the State of Texas, its successors and assigns, my entire interest in and the full and exclusive right to the INVENTIONS, the APPLICATION and all related applications (including all divisions, reissues, continuations, and extensions thereof) and all counterparts in other countries, and any and all Letters Patent (and certificates of invention or similar certificates) (herein PATENTS) which may be granted based upon the INVENTIONS or the APPLICATION or related applications or counterparts in all countries; said transfer and assignment being applicable throughout the world. I hereby authorize and request officials of patent offices in any and all countries of the world to issue any and all of the PATENTS, when granted, to HARC, its successors and assigns, as the assignee of my entire right, title, and interest in and to the same. I agree that I will communicate to HARC, or its representatives, any facts known to me respecting the invention; testify in any legal proceedings; sign all lawful papers; execute all divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of the PATENTS to be issued to HARC, make all rightful oaths; and generally do everything possible to aid HARC, its successors and assigns, to obtain and enforce proper protection for the INVENTION in any and all countries throughout the world. The APPLICATION is identified as:

Int'l Appl. No.: PCT/US94/12282

Int'l Filing Date: October 27, 1994

Docket No.: HARC0001

Country: United States

Title: Microfabricated Porous Apparatus for Discrete Detection of Binding Reactions

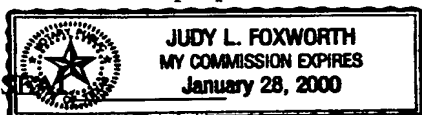
FULL NAME OF INVENTOR: Kenneth L. Beattie

Signature of Inventor: Kenneth L. Beattie

Address: 2 Hollymead  
The Woodlands, Texas 77381  
U.S.

STATE OF TEXAS  
COUNTY OF ~~HARRIS~~ MONTGOMERY

On January 23, 1996, the above-named inventor personally appeared before me and executed the foregoing instrument and acknowledged the same to be his/her free act and deed in and for the purposes set forth in said instrument.



Judy L. Foxworth  
Notary Public

My Commission Expires: 1 - 28 - 2000

## NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 4/10/96

A. ☒ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.  
B. ☒ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings:  
Black ink. Color.

☐ Not black solid lines. Fig(s) \_\_\_\_\_  
☐ Color drawings are not acceptable until petition is granted.  
Fig(s) \_\_\_\_\_

## 2. PHOTOGRAPHS. 37 CFR 1.84(b)

☐ Photographs are not acceptable until petition is granted.  
Fig(s) \_\_\_\_\_  
☐ Photographs not properly mounted (must use bristol board or photographic double-weight paper). Fig(s) \_\_\_\_\_  
☐ Poor quality (half-tone). Fig(s) \_\_\_\_\_

## 3. GRAPHIC FORMS. 37 CFR 1.84(d)

☐ Chemical or mathematical formula not labeled as separate figure.  
Fig(s) \_\_\_\_\_  
☐ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis.  
Fig(s) \_\_\_\_\_  
☐ Individual waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s) \_\_\_\_\_

## 4. TYPE OF PAPER. 37 CFR 1.84(c)

☐ Paper not flexible, strong, white, smooth, nonshiny, and durable.  
Sheet(s) \_\_\_\_\_  
☐ Erasures, alterations, overwritings, interlineations, cracks, creases, and folds copy machine marks not accepted. Fig(s) \_\_\_\_\_  
☐ Mylar, velum paper is not acceptable (too thin). Fig(s) \_\_\_\_\_

## 5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:

21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)  
21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)  
21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)  
21.0 cm. by 29.7 cm. (DIN size A4)

☐ All drawing sheets not the same size. Sheet(s) \_\_\_\_\_  
☐ Drawing sheet not an acceptable size. Sheet(s) \_\_\_\_\_

## 6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

## Paper size

21.6 cm. X 35.6 cm. (8 1/2 X 14 inches)	21.6 cm. X 33.1 cm. (8 1/2 X 13 inches)	21.6 cm. X 27.9 cm. (8 1/2 X 11 inches)	21.0 cm. X 29.7 cm. (DIN Size A4)
T 5.1 cm. (2")	2.5 cm. (1")	2.5 cm. (1")	2.5 cm.
L 64 cm. (1/4")	64 cm. (1/4")	64 cm. (1/4")	2.5 cm.
R 64 cm. (1/4")	64 cm. (1/4")	64 cm. (1/4")	1.5 cm.
B 64 cm. (1/4")	64 cm. (1/4")	64 cm. (1/4")	1.0 cm.

Margins do not conform to chart above.

Sheet(s) \_\_\_\_\_  
Top (T) \_\_\_\_\_ Left (L) \_\_\_\_\_ Right (R) \_\_\_\_\_ Bottom (B)

## 7. VIEWS. 37 CFR 1.84(h)

REMINDER: Specification may require revision to correspond to drawing changes.

☒ All views not grouped together. Fig(s) \_\_\_\_\_  
☒ Views connected by projection lines or lead lines.  
Fig(s) \_\_\_\_\_  
☐ Partial views. 37 CFR 1.84(h) 2

☒ View and enlarged view not labeled separately or properly.  
Fig(s) 105

☐ Sectional views. 37 CFR 1.84 (h) 3  
☐ Hatching not indicated for sectional portions of an object.  
Fig(s) \_\_\_\_\_

☐ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s) \_\_\_\_\_

## 8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)

☐ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) \_\_\_\_\_

## 9. SCALE. 37 CFR 1.84(k)

☐ Scale not large enough to show mechanism with crowding when drawing is reduced in size to two-thirds in reproduction.  
Fig(s) \_\_\_\_\_  
☐ Indication such as "actual size" or scale 1/2" not permitted.  
Fig(s) \_\_\_\_\_

## 10. CHARACTER OF LINES, NUMBERS, &amp; LETTERS. 37 CFR 1.84(l)

☐ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings).  
Fig(s) \_\_\_\_\_

## 11. SHADING. 37 CFR 1.84(m)

☐ Solid black shading areas not permitted.  
Fig(s) \_\_\_\_\_  
☐ Shade lines, pale, rough and blurred. Fig(s) \_\_\_\_\_

## 12. NUMBERS, LETTERS, &amp; REFERENCE CHARACTERS. 37 CFR 1.84(p)

☐ Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s) \_\_\_\_\_  
☐ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s) \_\_\_\_\_  
☐ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s) \_\_\_\_\_  
☐ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s) \_\_\_\_\_

## 13. LEAD LINES. 37 CFR 1.84(q)

☐ Lead lines cross each other. Fig(s) \_\_\_\_\_  
☐ Lead lines missing. Fig(s) \_\_\_\_\_

## 14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)

☐ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s) \_\_\_\_\_

## 15. NUMBER OF VIEWS. 37 CFR 1.84(u)

☐ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) \_\_\_\_\_  
☐ View numbers not preceded by the abbreviation Fig. Fig(s) \_\_\_\_\_

## 16. CORRECTIONS. 37 CFR 1.84(w)

☐ Corrections not made from prior PTO-948.  
Fig(s) \_\_\_\_\_

## 17. DESIGN DRAWING. 37 CFR 1.152

☐ Surface shading shown not appropriate. Fig(s) \_\_\_\_\_  
☐ Solid black shading not used for color contrast.  
Fig(s) \_\_\_\_\_

## COMMENTS:

ATTACHMENT TO PAPER NO. \_\_\_\_\_

REVIEWER: WAS

DATE: 6/20/96

Applicant's Copy





UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/631,751	04/10/96	KEATTIE	94R00001

VINSON A. ELKINS  
1435 PENNSYLVANIA AVENUE NW  
SUITE 800  
WASHINGTON DC 20004-1008

18M1/1126

EXAMINER

BAKALYAR, H

ART UNIT PAPER NUMBER

1818

6

DATE MAILED: 11/26/96

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 4/10/96
- ☐ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire \_\_\_\_\_ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-20 is/are pending in the application.
- Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☐ Claim(s) \_\_\_\_\_ is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☒ Claims 1-20 are subject to restriction or election requirement.

Application Papers

- ☐ See the attached \_\_\_\_\_ Patent Drawing Review, PTO-948.
- ☐ The drawing(s) \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some ☐ None of the CERTIFIED copies of the priority documents have been:
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) \_\_\_\_\_
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

SENT TO HUSON  
FOR OFFERING  
12/18/96  
20



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

APPLICATION NUMBER FILING DATE FIRST NAMED APPLICANT ATTORNEY DOCKET NO.

VINSON & ELKINS  
1111 CONNORVILLE AVENUE NW  
SUITE 800  
WASHINGTON DC 20004-1008

18M1/0513

RECEIVED  
MAY 20 1997

EXAMINER

RAKALYAR, H

ART UNIT PAPER NUMBER

1818

9

Docket Sec.  
Vinson & Elkins

DATE MAILED:

05/13/97

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

Response:  
Sept 13, 1997 (1st ext)  
ENTERED IN DOCKET  
09/19/97

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 3/18/97
- ☐ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1835 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-20 is/are pending in the application.
- Of the above, claim(s) 12, 17-20 is/are withdrawn from consideration.
- ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- ☒ Claim(s) 1-11, 13-16 is/are rejected.
- ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- ☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a))

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of Reference Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 4/13
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

THIS PAGE IS FOR THE EXAMINER'S USE ONLY. IT IS NOT TO BE REPRODUCED OR DISTRIBUTED OUTSIDE THE PATENT AND TRADEMARK OFFICE.

EXAMINER'S USE ONLY

DATE OF ACTION: 05/13/97

REASON FOR ACTION: 1.136(a)

REMARKS: (1) Claims 1-11, 13-16 are rejected under 35 U.S.C. § 103 as being obvious over the prior art. (2) Claims 12, 17-20 are withdrawn from consideration. (3) Claims 1-20 are pending in the application.

EXAMINER: RAKALYAR, H

ART UNIT: 1818

PAPER NUMBER: 9

- SEE OFFICE ACTION ON THE FOLLOWING PAGES -

Art Unit: 1818

1. Applicant's election without traverse of Group I, claims 1-16, and the species claimed by claims 10-11 (as opposed to the species of claim 12), in Paper No. 8 is acknowledged.

### *Specification*

2. The use of trademarks such as DRIERRITE, page 20, line 15; MICROLAB, page 20, line 29; have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### *Claim Rejections - 35 USC § 112*

3. Claims 1-11 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- a. Claim 1 is unclear and incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2173.05(I). It is unclear how the recited pieces of the claimed device fit together. For example, some omitted structural cooperative relationships are: the relationship of the first and second surfaces (e.g. are they opposite to each other?); the location of the

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detecting means in relation to the first and second surfaces in both prior art device and improved device; the location to which test sample is added in both prior art device and improved device, the relationship between the location of the detecting means and the test sample in both prior art device and improved device; the location of the biomolecules in relation to the improved device that comprises discrete and isolated regions.

b. The recitation of "addressing" in line 4 of claim 1 is vague and indefinite. The meaning of the term is not clear.

c. The recitation of "essentially homogeneous" in line 7 of claim 1 is vague and indefinite. The term "essentially" is not an exclusive term, and therefore it is not clear what other components may be included in the "essentially homogeneous" sample.

d. The recitation of "information" in line 10 of claim 1 is vague and indefinite. It is unclear as to what "information" is meant to encompass. Is "information" referring to the detectable signal? Further, what data is encompassed by information? For example, molecular weight of a component in a test sample, or the complete chemical constitution of the test sample or other?

e. The recitation of "identifying or otherwise characterizing" in line 11 of claim 1 is vague and indefinite. Identifying and otherwise characterizing are two completely different concepts. Further, it is unknown what is encompassed by "otherwise characterizing".

f. The recitation of "second surface" in line 15 of claim 1 is vague and indefinite. It is noted that there is no recitation of a first surface in the claim.

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g. The recitation of "binding reaction" in line 15 of claim 1 is vague and indefinite. It is unclear what type of binding reactions are encompassed by the claim: e.g. covalent, non-covalent, ionic, chelation, etc..

h. The relationship between "binding reaction" in lines 5, 8-9 and 15 is unclear. e.g. it is unknown whether "the binding reaction" of line 5 is the same binding reaction ("a binding reaction") of lines 8-9; further, it is not known to which of these reactions "said binding reaction" of line 15 refers.

i. The relationship between the "discrete and isolated regions" of line 2 and the "discrete and isolated regions" of the improvement in line 13 is not clear. For example, it is not known if they are the same discrete and isolated regions.

j. There is no antecedent basis for "the detection" in line 8. Further it is unknown what is encompassed by "the detection", e.g. fluorescent, colorimetric, etc..

k. There is no antecedent basis for "the molecular species".

4. Claims 2-11, 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-11, 13 are indefinite in reciting "the improvement" in the preamble as the claims are drawn to a microfabricated device, not an improvement per se.

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5. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is vague and indefinite because base claim 1 recites that the discrete and isolated regions extend through the substrate (e.g. through both faces) whereas claim 4 recites that the discrete and isolated regions only extend to one face of the substrate (e.g. nanoporous glass wafer).

6. Claims 9 and 13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 13 are indefinite in that it is unclear how the additional recited process limitation limits the product, e.g. the microfabricated device.

7. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "first surface" in line 2 of claim 9 lacks clear antecedent basis in claim 1.

8. Claims 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The recitations of "high density and ultra-high density" in line 1 of claims 5 and 6 are vague and indefinite. The terms lack proper antecedent basis in claims 1 and 4. It is suggested the phrase similar to --wherein said array is a high (or ultrahigh) density array-- be used to obviate the rejection.

9. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear where the triethylene glycol phosphoryl units are incorporated.

10. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 14 is unclear and incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2173.05(I). It is unclear how the recited pieces of the claimed device fit together. For example, some omitted structural cooperative relationships are: the location of the detection means in relation to the first and second surfaces; the relationship of the first and second surfaces (e.g. are they on opposite sides of the substrate?); the location to which test sample is added.

b. The recitation of "homogeneous samples of a predetermined set of biomolecules" in line 5 of claim 14 is vague and indefinite. It is unclear how the samples can be homogenous (or

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substantially homogeneous) as the term "set" implies a group comprised of different molecules. Furthermore, the use of the term "samples" is confusing, as "sample" is routinely used in the art to describe a test or experimental entity, not the standard or detecting molecule.

c. The recitation of "substantially homogeneous" in line 5 of claim 14 is vague and indefinite. The term "substantially" is not an exclusive term, and therefore it is not clear what other components may be included in the "substantially homogeneous" sample.

11. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said molecular species" in line 2 of claim 16 has no clear antecedent basis in claim 14.

12. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The relationship between the substrate of claim 1 and the glass substrate of claim 10 is unclear. It is unknown whether the claims are referring to the same substrate.

13. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.



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Claim 13 implies but does not state that the binding reaction is a hybridization reaction and is confusing in (1) reciting components which are not part of the device, e.g. in particular the labelled reagents and (2) the detection of radioactivity with a CCD.

14. Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims should begin with --The-- for consistency.

*Claim Rejections - 35 USC § 102*

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-2, 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Saiki et al PNAS (1989) 86 pages 6230-6234.

Saiki et al teach immobilization of oligonucleotide probes to a membrane in spots (see Figures 2 and 3). Note that the membrane reads on a substrate which has regions that extend through the substrate such that the test sample is capable of penetrating therethrough during the course of the binding reaction because membranes contain pores. In addition, the peroxidase label and leuco dye read on the detection means.

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*Claim Rejections - 35 USC § 103*

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 1-11, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815).

Pirrung et al teach synthesis of oligonucleotide arrays to make chemically diverse oligomers for screening for biological activity. This reference teaches that essentially any conceivable substrate may be used and that it may be desirable to physically separate synthesis regions for different polymers with well, raised regions, etched trenches or the like (e.g. col 11, lines 16-36; col 7, lines 49-57). Pirrung et al teach that the surface of the substrate is preferably provided with a layer of linker molecules, which are of a sufficient length to permit polymers in a completed substrate to interact freely with molecules exposed to the substrate (see paragraph bridging columns 11-12) and the linker molecules are attached to glass surfaces via siloxane bonds (col 12, lines 30-40). In addition, on col 20, lines 1-26 Pirrung et al teach how one would synthesize all sixteen dinucleotides from four bases (reads on a fully degenerate set of oligonucleotides) each unique to a defined position in the array, and teaches the use of a microscope and fluorescent label to detect the binding reaction (reads on a detecting means which

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determines and reports the extent of a binding reaction, and as a charge-coupled device counts photons, fluorescence microscopy reads on detection via a charge coupled device. In the alternative, such a device is an obvious variant as both the instant microscopy and charge-coupled devices detect photons, and charge-coupled devices were well known at the time of invention). One of skill in the art would expect the oligonucleotides to be substantially homogeneous within a single position in the array due to the disclosed method of preparation of the array.

Pirrung et al fail to specifically teach the use of substrates which have discrete and isolated regions that extend through the substrate, such as nanoporous glass.

Tonucci et al teach nanochannel filters (nanoporous wafer-like glass filters, see for example, Abstract) which have channels therethrough having an average diameter of less than one micron and in which the channels are present in high density (see col 3, lines 46-51 and Figure 5). Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels which can reach  $10^{12}/\text{cm}^2$  (col 5, lines 51-66) (reads on a high or ultra-high density array of channels). This reference teaches that when a thin section of the nanochannel filter is acid etched completely through, it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter (reads on comprising a means for providing fluidic flow). In addition, this reference teaches that the nanochannel filter may be used in a variety of filtering conditions, and that the channels themselves may be straight or curved, (therefore one of skill in the art would expect channel shape was not critical), and may have a chemical lining on the walls (col 6, lines 24-30).

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Guirguis teaches the advantages of using microporous membranes in immunoassays (which would apply to any specific binding assays, such as hybridization assays), in that filtration minimizes the diffusion limitation of the reaction rate due to the flow of reagents through the receptor-bearing membrane solid phase and the high ratio of microporous membrane surface to liquid volume (col 3, lines 12-29). In addition, this reference teaches that membrane substrates overcome many of the problems inherent in solid phase immunoassays as they combine the qualities of a solid substrate with a range of expanded capabilities and, due to their porosity and consequential large surface area, have a high binding capacity, which is measured by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface (col 2, lines 15-23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the bimolecular arrays of Pirrung et al because this would allow for easy separation of free and bound target and because of the increased available surface area which allow for greater sensitivity, both well known advantages of filtration-based specific binding assays as well as for the teaching of Guirguis that membranes (which would include filters) have a high binding capacity, which is increased by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface. Further, Tonucci teaches that when a thin section of the nanochannel filter is acid etched completely through it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter, and that the channels may

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have chemical lining on the walls (reads on oligonucleotide lining). In addition, it would have been obvious to use any desired shape of the wells and any desired density of the wells because Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels and the high packing of the channels, which can reach  $10^{12}/\text{cm}^2$ , and that the shape of the channels is not critical. It is noted that Applicant has not pointed to the criticality of any of the recited dimensions of the regions (reads on channels) nor their packing density, therefore, such limitations are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results. One of ordinary skill in the art at the time the invention was made would have been motivated to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the bimolecular arrays of Pirrung et al because of the expectation of successfully making a high density, highly-sensitive device which would allow the simultaneous testing of multiple chemically diverse oligonucleotides for biological activity such as specific binding, or the ability to hybridize to test substances.

19. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815), as applied to claims 1-11, 13-15, in further view of the known fact presented in the instant specification and Parham et al, BBRC vol 80 no 1 (1978) pages 1-6.

It may be determined that the siloxane bonds of Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815) which attach the

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polynucleotides to glass is differ from the bonds made by reaction of a terminal primary amine derivative of said polynucleotide to epoxysilane derivitized glass, and that triethylene glycol units are not incorporated.

However, page 23, line 25 through page 24, line 19 disclose that the chemistries involved in such reactions are well known for coupling amine-containing oligomers to glass.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to attach the polynucleotides to glass is differ by reaction of a terminal primary amine derivative of said polynucleotide to epoxysilane derivitized glass, and thereby incorporating triethylene glycol units because such chemistries are well known. One of ordinary skill in the art at the time the invention was made would have been motivated to attach the polynucleotides to glass is differ by reaction of a terminal primary amine derivative of said polynucleotide to epoxysilane derivitized glass, and thereby incorporating triethylene glycol units because of the expectation of successfully attaching polynucleotide to the device taught by the combination of Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815).

20. Claims 1-11, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al, Clinical Chemistry 1993 in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815).

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Beattie et al teach genosensors comprising all oligonucleotide probes of a given length (e.g. 8-mer is 65,536 distinct probes, reads on fully degenerate) and teach DNA probe attachment to a glass surface through the use of siloxysilane and triethylene glycol phosphoryl spacers and teaches different methods such as the measurement of impedance of CCD arrays.

However, the reference differs from the instant invention in that it does not specifically teach the use of substrates which have discrete and isolated regions that extend throughout the substrate, such as nanoporous glass wafers.

Tonucci et al teach nanochannel filters (nanoporous wafer-like glass filters, see for example, Abstract) which have channels therethrough having an average diameter of less than one micron and in which the channels are present in high density (see col 3, lines 46-51 and Figure 5). Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels which can reach  $10^{12}/\text{cm}^2$  (col 5, lines 51-66) (reads on a high or ultra-high density array of channels). This reference teaches that when a thin section of the nanochannel filter is acid etched completely through, it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter (reads on comprising a means for providing fluidic flow). In addition, this reference teaches that the nanochannel filter may be used in a variety of filtering conditions, and that the channels themselves may be straight or curved, (therefore one of skill in the art would expect channel shape was not critical), and may have a chemical lining on the walls (col 6, lines 24-30).

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Guirguis teaches the advantages of using microporous membranes in immunoassays (which would apply to any specific binding assays, such as hybridization assays), in that filtration minimizes the diffusion limitation of the reaction rate due to the flow of reagents through the receptor-bearing membrane solid phase and the high ratio of microporous membrane surface to liquid volume (col 3, lines 12-29). In addition, this reference teaches that membrane substrates overcome many of the problems inherent in solid phase immunoassays as they combine the qualities of a solid substrate with a range of expanded capabilities and, due to their porosity and consequential large surface area, have a high binding capacity, which is measured by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface (col 2, lines 15-23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the genosensor of Beattie et al because this would allow for easy separation of free and bound target and because of the increased available surface area which allow for greater sensitivity, both well known advantages of filtration-based specific binding assays as well as for the teaching of Guirguis that membranes (which would include filters) have a high binding capacity, which is increased by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface. Further, Tonucci teaches that when a thin section of the nanochannel filter is acid etched completely through it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter, and that the channels may



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### *Conclusion*

21. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Column 10, lines 12-23 of U.S. Patent 5,231,035 teaches a binding assay wherein ligands are bound to a glass membrane, which is placed into a filter well.

22. Any inquiry concerning this communication should be directed to Heather Bakalyar at telephone number (703)305-7143.

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The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached on (703) 308-4310. The fax phone number for this Group is (703)305-7939.

23. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group 1800 receptionist whose telephone number is (703)308-0196.

Heather Bakalyar, Ph.D.

*Heather Bakalyar*

5/9/97

*Carol A. Spiegel*  
CAROL A. SPIEGEL  
PRIMARY EXAMINER  
GROUP 1800